REMARKS/ARGUMENTS

1. Status of Claims

Claim 29 has been amended, claims 1-28 and 35-38 has been withdrawn with traverse, and claims 29-34 are pending in the instant application. Support for the amendment to claim 29 can be found in the specification and claims as originally filed. The amendments to the pending claims were made to clarify the scope of coverage and more particularly point out and distinctly claim the present invention. These amendments are made without prejudice, do not constitute amendments to overcome any prior art rejections, and do not present any new matter. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

2. Rejection under 35 U.S.C. § 112, second paragraph

a. Claims 29-34 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Patent Office asserts that "claim 29 is drawn to a method comprising the step of treating a subject with an anti-EGFR antibody when HER 3 expression levels in the cell are low." The Patent Office further asserts that "there is no definition in the specification for what is meant by 'low' expression levels of HER3." Applicants respectfully traverse the rejection.

The methods and criteria for determining relative levels of HER3 expression are clearly defined in the specification. For example, a low level of expression is defined as an OD measurement of less than 9 or 10 as determined by quantitative immunohistochemistry. *See* specification, page 11, lines 14-16 ("Thus, the level of expression and/or activation in a cell can be determined by, for example, quantitative immunohistochemistry. In this case, the level of expression of HER1, HER2, and/or HER3 is considered to be low if the OD is less than 9."). *See also* id. at Table II (defining low expression level of HER2 to be an OD less than 10). Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

b. Claims 29-34 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Patent Office asserts that "claim 29 is drawn to a method comprising the step of determining expression of HER3 in cells from a subject instead of determining

levels of HER3 in cells from cancer." The amendment to claim 29 obviates this rejection. Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

3. Rejection under 35 U.S.C. § 112, first paragraph

a. Claims 30, 32 and 34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not set forth in such a way as to enable one skilled in the art to make and/or use the invention. The Patent Office asserts that "the specification fails to describe how to make the ABX-0303 monoclonal antibody." The Patent Office further asserts that U.S. Patent 6,235,883 (the "'883 patent"), incorporated by reference in the present specification, neither provide sufficient disclosure for how to make ABX-0303, nor even refers to hybridoma E7.6.3, used to produce the ABX-0303 antibody. Applicants respectfully traverse the rejection.

First, the production of the ABX-0303 monoclonal antibody, which is also known as ABX-EGF as outlined in the specification on page 3, lines 21-26, is well known to those with skill in the art. The Patent Office states in the instant action that "evidence must be provided that the ABX-0303 monoclonal antibody is well known." The Applicants, however, respectfully disagree with the Office Action's characterization of the '883 patent. First, the '883 patent clearly refers to and teaches hybridoma E7.6.3. *See, e.g.*, the '883 patent, col. 28, line 62-col. 29, line36 and Figures 29-32. Moreover, the '883 patent provides more than sufficient disclosure on both the hybridoma E7.6.3, as well as the ABX-0303 antibody itself. For example, Figure 29 provides "an amino acid sequence of a heavy chain immunoglobulin molecule that is secreted by the hybridoma E7.6.3." *See* id., col. 29, lines 14-16, Figure 29. Also, Figure 30 provides the nucleotide sequence of the cDNA encoding the heavy chain immunoglobulin molecule of Figure 29. *See* id., col. 29, lines 23-25, Figure 30. In addition, Figures 31 and 32 provide an amino acid sequence and the nucleotide sequence of the cDNA encoding the kappa light chain immunoglobulin molecule that is secreted by the hybridoma E7.6.3. *See* id., col. 29, lines 14-16, Figure 26-36. It is clear, therefore, that from the teaching of the '883 patent, not

only the ABX-0303 patent was well known at the time of filing of the present application, hybridoma E7.6.3 was also well know.

Furthermore, as even noted by the Patent Office in the instant action, Yang, et al. teaches the production, characterization, and use of ABX-EGF, which is the ABX-0303 antibody of the instant application. It is clear, therefore, that the production of the ABX-0303 antibody of the instant application is well known to those of skill in art, and thus claims 30, 32, and 34 do not require undue experimentation and are fully enabled.

Finally, it is important to note that the present claims are not drawn to the antibody ABX-0303, to hybridoma E7.6.3, or to the antibodies produced by hybridoma E7.6.3. Instead, the present claims are drawn to methods of using the ABX-0303 antibody. In fact, the '883 patent claims the very antibodies for which a use is described in the present invention, and because the '883 patent is presumed to be enabled, the use of the patented antibodies in the present invention surely is also enabled.

Applicants respectfully request reconsideration and withdrawal of the rejection.

b. Claims 29-34 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not set forth in such a way as to enable one skilled in the art to make and/or use the invention. The Patent Office asserts that "the specification while being enabling for methods of treating a subject with cancer that express EGFR, does not reasonably provide enablement for treating a subject with any type of cancer." The amendment to claim 29 obviates this rejection. Thus, the Applicants respectfully request reconsideration and withdrawal of the rejection.

4. Rejection under 35 U.S.C. § 103

a. Claims 29, 31 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herbst in view of Xia. The Applicants respectfully traverse the rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

In order to establish a *prima facie* case of obviousness the Patent Office must establish that the prior art references contain *all* the claim limitations. The combination of references cited with particularity by the Patent Office does not contain the following limitation of claim 29: "treating the subject with an anti-EGFR antibody when HER3 expression levels are low." The Patent Office cites Herbst as teaching methods of targeting the EGFR when HER1 levels are high. However, the Patent Office does not even suggest that Herbst teaches the claim limitation of "determining the level of expression of HER3 in the cells from the cancer, and treating the subject with an anti-EGFR antibody when HER3 expression levels are low." Instead, the Patent Office simply asserts that Herbst teaches using an "anti-EGFR antibody to treat a cancer, such as head and neck cancer." What Herbst does teach is treating only certain head and neck cancers, specifically those that express high levels of HER1, with anti-EGFR antibodies, not treating head and neck cancer with anti-EGFR antibodies generally, much less when HER3 expression levels are low.

The deficiencies of Herbst are not overcome by the citations of Xia. In fact, the Patent Office concedes that Xia does not teach or suggest that instant invention, for example, by clearly stating in the instant action that Xia teaches that "head and neck [cancer] do not tend to express HER3,"and that "in head and neck [cancer], HER3 is not a useful prognostic indicator." In fact, these statements by the Patent Office actually demonstrate that Xia teaches away from the instant invention of using low levels of HER3 as an indicator for use of an anti-EGFR antibody and in particular claim 29 which recites "determining the level of expression of HER3 in the cells from the cancer, and treating the subject with an anti-EGFR antibody when HER3 expression levels are low." Moreover, the Patent Office specifically acknowledges that "Xia fails to teach treating cancers with low HER3 with an anti-EGFR antibody" and thus does not teach all of the claim limitation of claim 29.

In fact, far from teaching anything about treating cancers with low HER3 with an anti-EGFR antibody irrespective of HER1 expression levels, the combination of Herbst with Xia would actually lead one of skill in the art to the conclusion that anti-EGFR antibodies will *not* be effective at treating head and neck cancers *unless* said cancer cells

also express high levels of HER1. Applicants respectfully submit that, despite the Patent Office's assertion, it has not demonstrated that the prior art references alone or in combination could be used to arrive at the claimed invention. As rejected claims 31 and 33 depend from claim 29, thereby sharing the above limitations, the cited references also cannot render claims 31 and 33 obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

b. Claims 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Herbst in view of Xia and further in view of Yang. The Applicants traverse the rejection.

As explained above, the combination of Xia and Herbst references cited by the Patent Office does not contain all of the claims limitations of claim 29. The combination of references does not disclose at least the following limitation of claim 29: "determining the level of expression of HER3 in the cells from the cancer, and treating the subject with an anti-EGFR antibody when HER3 expression levels are low." In fact, the references cited by the Patent Office teach away the invention of claim 29.

The further citation of Yang does not cure the deficiencies of Xia and Herbst. Yang teaches the production, characterization, and use of the ABX-EGR antibody. Yang does not teach, much less suggest, determining the level of expression of HER3 in the cells from the cancer. As a result, the combination of the cited references does not teach or suggest all of the claim limitations. Thus, the Patent Office has not established a *prima facie* case of obviousness of claim 29 based on the cited references. As rejected claims 30-34 depend from claim 29, thereby sharing the above limitations, the cited references also cannot render claims 31 and 33 obvious. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

Based on all of the above, the Applicants believe the claims are now allowable. If there are any questions or comments regarding this response, the Patent office is encouraged to contact the undersigned agent as indicated below.

Respectfully submitted,

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/Andrew W. Williams/
Andrew W. Williams
Registration No. 48,644

McDonnell Boehnen Hulbert & Berghoff, LLP
300 South Wacker Drive
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002